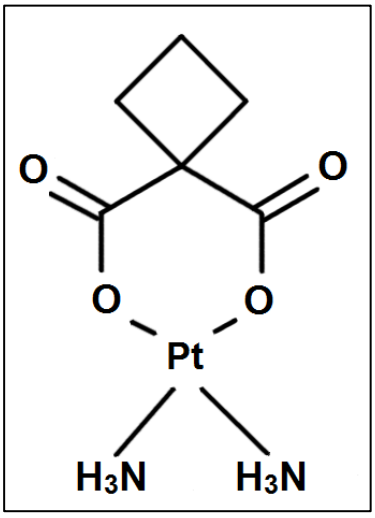
CARBOPLATIN (CBDCA) DRUG PRODUCT HAS BEEN REPORTED USEFUL FOR TREATING OSTEOSARCOMA IN DOGS

KEY POINTS:

- Carboplatin (CBDCA) has been reported to be effective as a single agent chemotherapy treatment for dogs with osteosarcoma (OSA) before, concurrently, or after amputation of the tumor-bearing limb.[1,2,3]
- At a dose of 300 mg/m^2 given every 21 days, carboplatin has been reported to have low likelihood of chemotherapy induced toxicity.[1,3]
- The most frequently observed dose-limiting toxicity has been myelosuppression, specifically neutropenia. Toxicities were often reversible with a short delay of treatment.[1,3]

BACKGROUND:

Carboplatin (CBDCA) is a second-generation platinum antineoplastic agent. Carboplatin produces interstrand and intrastrand crosslinks in DNA, which inhibit DNA replication, RNA transcription, and protein synthesis. Carboplatin produces similar cross-linking as cisplatin (CDDP), resulting in equivalent lesions and biological effects. However, aquation occurs at a slower rate for carboplatin than cisplatin. The slower rate appears to be the primary reason that carboplatin has fewer reported adverse effects in dogs compared to cisplatin. Carboplatin is cell-cycle nonspecific.[4]



Carboplatin has been reported to be useful in treating OSA in dogs before, concurrently, or after amputation of the tumor-bearing limb. Carboplatin is offered by Amatheon as a generic drug in three sizes. The injectable single dose vials are available in 50mg, 150 mg, and 450 mg per vial.

CARBOPLATIN HAS BEEN REPORTED TO BE EFFECTIVE IN MANAGING OSA IN DOGS.[1,2]

Study 1. In this prospective clinical trial, 48 dogs with appendicular OSA were treated with amputation and postoperative carboplatin. Carboplatin was administered at 300 mg/m^2 IV every 21 days for a total of 4 doses.[1]

- 34 dogs completed the assigned 4-cycle treatment protocol.
- Median disease free interval (DFI) for the 34 dogs completing the protocol was 327 days.
- Median survival for the 34 dogs completing the protocol was 383 days.
    - Results indicated that dogs treated with carboplatin and amputation are 2.1 times more likely to survive than dogs treated by amputation alone **[Figure 1]**.

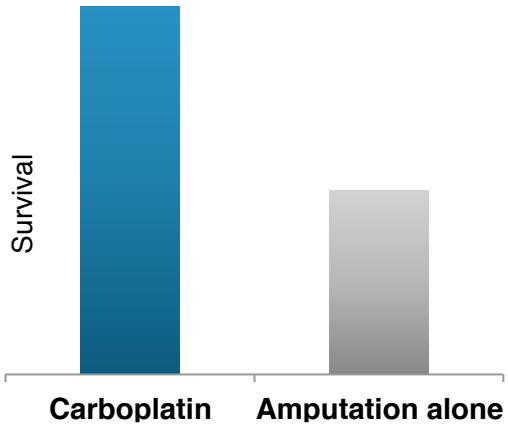


Figure 1: Comparison of survival times of dogs treated with carboplatin and amputation alone.

- 14 dogs had chemotherapy discontinued.
    - The primary reason for discontinuation was metastases (11 dogs).
- 14 delays in treatment occurred.
    - Treatment was discontinued because of neutropenia (13 dogs) and neutropenia and thrombocytopenia (1 dog).
    - Delays in treatment were never longer than 7 days.
- Dogs with lower body weights (<40 mg) had significantly higher DFI (median 337 days) and survival times (median >400 days) than larger dogs (DFI, 109 days; survival time, 242 days).

Study 2. In this preclinical study, 54 dogs with appendicular OSA were randomized into a treatment with a long-acting analogue of somatostatin (OncoLAR) and carboplatin chemotherapy or a control group receiving placebo and carboplatin. Carboplatin was administered every 21 days at a dose of 300 mg/m^2 by slow IV infusion, starting 7 days before amputation of the tumor-bearing limb.[2]

- Median DFI was 215 days and overall survival was 242 days for the 23 dogs in the OncoLAR and carboplatin treatment-received group.
- Median DFI was 196 days and overall survival was 230 days for the 22 dogs in the placebo and carboplatin treatment-received group.
    - No significant differences were seen in DFI or survival in the two populations.
- Serum insulin-like growth factor I (IGF-I) concentrations in dogs treated with OncoLAR were reduced by 43% without toxicity.
    - Authors reported that this suppression of serum IGF-I was insufficient to increase primary tumor apoptosis or necrosis above that induced by carboplatin alone.

CARBOPLATIN TREATMENT AT 300 mg/m^2 RESULTED IN LOW LEVELS OF OBSERVED TOXICITY.[3]

Study 3. In this dose-escalation study, 30 dogs with malignant neoplasms were treated with carboplatin via IV infusion every 21 days at a dose ranging from 100–400 mg/m^2. The mean number of treatment cycles was 3.1 (range, 1–11 cycles).

- MOD50 (dose resulting in a 50% incidence of moderate toxicity) for the first course of treatment was 340 mg/m^2.
    - MOD50 for cumulative treatment was 327 mg/m^2.
- SEV5 (dose resulting in a 5% incidence of severe toxicity) for the first course of treatment was 278 mg/m^2.
    - SEV5 for cumulative treatment was 231 mg/m^2.
- 3 of the 18 dogs that had measurable tumors at the beginning of treatment showed partial response.
- 5 of the 18 dogs that had measurable tumors at the beginning of treatment had stable response.

CONCLUSIONS

These clinical studies report that carboplatin has a high response rate and is generally well-tolerated, supporting the use of carboplatin in treating OSA in dogs. Authors saw infrequent toxicity. Toxicities that were observed were often reversible with a short delay of treatment. In addition, the results also show that carboplatin treatment has significantly extended the survival times of dogs with OSA beyond the survival times previously reported for amputation alone.

TREATMENT RECOMMENDATIONS

The finding from these studies demonstrate how carboplatin has been used effectively in the treatment of dogs with OSA. At a dose of 300mg/m^2 every 21 days, authors reported a high response rate and infrequently observed toxicities. Therefore, carboplatin can be considered as part of a treatment regimen for OSA before, concurrently, or after amputation of the tumor-bearing limb. Carboplatin also serves as a good alternative to cisplatin. Efficacy of carboplatin has been reported to be comparable to two or four doses of cisplatin, and reported DFI and survival times compared favorably with previously reported times for dogs treated with cisplatin.[1]

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[1] Bergman, P. J., et al (1996). Amputation and carboplatin for treatment of dogs with osteosarcoma: 48 Cases (1991 to 1993). *Journal of Veterinary Internal Medicine, 10*(2), 76–81

[2] Khanna, C., et al. (2002). A randomized controlled trail of octreotide pamoate long-acting release and carboplatin versus carboplatin alone in dogs with naturally occurring osteosarcoma: Evaluation of insulin-like growth factor suppression and chemotherapy. *Clinical Cancer Research, 8*, 2406–2412

[3] Page, R. L., et al. (1993). Pharmacokinetic and Phase I evaluation of carboplatin in dogs. *Journal of Veterinary Internal Medicine, 7*(4), 235–239.

[4] Plumb, D. C., (2011). Carboplatin. In *Plumb's Veterinary Drug Handbook* (7th ed.). Vin Foundation.